

A Convenient Method for Carbon Extension of Acetals and Aldehydes by the Use of Ketenedithioacetal and Nucleophiles

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A convenient method for carbon extension of acetals and aldehydes has been established consisting of combining a ketenedithioacetal **1** and nucleophiles such as alkyl- and alkynylmetal, metal enolate, and hydride. Acetals and aldehydes react with **1** in the presence of TMSOTf, and the successive addition of nucleophiles affords the corresponding β -alkoxy and β -siloxy dithioacetals in good yields.

Carbon chain extension is of fundamental importance in synthetic organic chemistry, and a variety of nucleophiles such as organometallics and keteneacetals have been employed in effective carbon-carbon bond formation. Ketenedithioacetals, which are easily prepared by using CS₂ in good yield,¹ have the specific property of the stabilizing effect of sulfur on positively and negatively charged α -carbon atoms and also on α -carbon radicals.² For this reason, ketenedithioacetals react readily with anionic,³ cationic,⁴ and radical⁵ species or undergo cycloaddition reactions.⁶ Therefore, ketenedithioacetals are useful intermediates in synthetic organic chemistry. However, there have been few reports concerning their Lewis acid-promoted reaction with acetals or aldehydes, since ketenedithioacetals easily polymerize under such acidic conditions.⁷

Recently, a novel method for the synthesis of thiols from the corresponding olefins by using thiocarbonates and Ti(IV) halides was reported from our laboratory.⁸ While screening similar types of reactions, acetal **2** was found to react with ketenedithioacetal **1** in the presence of TiCl₄ to afford thioester **4**. The formation of **4** is explained by considering the initial formation of intermediate **3**, which is stabilized by the neighboring sulfur atoms. The reaction of **3** with various nucleophiles was investigated, and β -alkoxy dithioacetals **5** (a masked carbonyl compound) were obtained in good yield after optimization of the reaction conditions (Figure 1). In this communication, we would like to report a convenient method for carbon extension that affords various dithioacetals either from acetal or aldehyde by a two-step sequence reaction, namely, 1) TMSOTf-mediated addition of ketenedithioacetal and 2) successive addition of nucleophile in a one-pot operation.

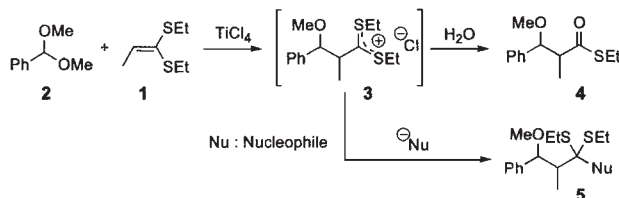


Figure 1.

As the initial formation of sulfur-stabilized intermediate **3** was thought to be essential, several Lewis acids such as TMSOTf, Sn(OTf)₂, Mg(OTf)₂, TiCl₂(OTf)₂, and BF₃·OEt₂ were screened

as a promoter for the addition of ketenedithioacetal **1** to benzaldehyde dimethylacetal **2**. TMSOTf was found to be most effective for the promotion of the above reaction. Next, several nucleophiles were used as alkylating reagents of the intermediate **3** under the reaction conditions as listed in Table 1. Higher-order cyanocuprate R₂Cu(CN)Li₂ gave far better results compared to Grignard reagent and alkyllithium (Table 1, Entries 1–3). Then, effect of solvents was examined by using dimethylcyanocuprate in the second step. The reaction proceeded smoothly either in toluene or CH₂Cl₂ to afford dithioacetal **6** in 74% or 70% yield respectively, by a two-step sequence reaction (Table 1, Entries 4 and 5). However, other solvents such as CHCl₃, THF, and Et₂O were not effective.

Table 1. Effect of nucleophiles and solvents

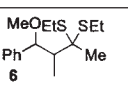
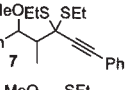
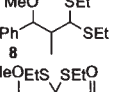
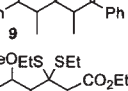
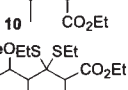
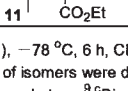
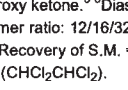
Entry	Nucleophile	Yield /%
1	MeLi	complex mixture
2	MeMgBr	32
3	Me ₂ CuLi ^a	41
4	Me ₂ Cu(CN)Li ₂	72 (74) ^b
5 ^c	Me ₂ Cu(CN)Li ₂	70

^aPrepared from CuI and 2MeLi, ^bThe first step: 0.5 h, ^cSolvent: CH₂Cl₂

In order to expand the scope of the present carbon extension reaction, several other nucleophiles were screened in the second step under the reaction conditions shown in Table 2. When either higher-order cyanocuprate or lithium acetylide was used, the corresponding dithioacetal (a ketone equivalent) were obtained in good yields (Table 2, Entries 1 and 2). When reducing reagents such as NaB(CN)H₃, L-Selectride, LiAl(O^tBu)₃H, and Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride) were examined as hydride sources, Red-Al was found to be the most effective and afforded the dithioacetal, an aldehyde equivalent, in high yield (Table 2, Entry 3). Furthermore, β -carbonyl dithioacetals were obtained in good yields on treatment with metal enolates such as lithium enolate and sodium malonate (Table 2, Entries 4–6). As well as acetal, aldehyde **12** also reacted with **1** to afford the desired β -siloxy dithioacetal in good yield (Scheme 1). In all cases, the isolated yields were lower than those determined by NMR analysis due to the instability of the formed dithioacetals either under acidic or basic conditions (Table 2, Entry 4).

Thus, an efficient carbon extension reaction using ketenedithioacetal has been established. It is interesting to note that the highly functionalized dithioacetals can be obtained from acetal or aldehyde in a one-pot procedure by TMSOTf-mediated reaction of ketenedithioacetal, followed by the addition of nucleophiles such as alkyl- and alkynylmetal, metal enolate, and hydride. This

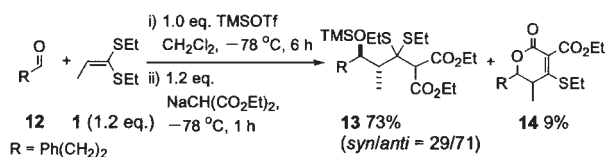
Table 2. Synthesis of dithioacetals using various nucleophiles

Entry	R	Nucleophile	Product	Yield /% (syn/anti) ^{b,c}
1	Ph	Me ₂ Cu(CN)Li ₂		74 (20/80)
2	Ph	Li-C≡C-Ph		81 (39/61)
3	Ph	Red-Al ^e		85 (32/68)
4	Ph			78 ^d [90 ^g]
5	Ph	NaCH(CO ₂ Et) ₂		83 (32/68)
6 ^a	Ph(CH ₂) ₂	NaCH(CO ₂ Et) ₂		68 ^f (38/62)

^aReaction conditions: i) TMSOTf (1.0 eq.), -78 °C, 6 h, CH₂Cl₂, ii) NaCH(CO₂Et)₂ (1.2 eq.), -78 °C, 2 h. ^bStereochemistry of isomers were determined by derivatization to the corresponding β-hydroxy ketone. ^cDiastereomer ratio determined by NMR analysis. ^dDiastereomer ratio: 12/16/32/40. ^eSodium bis(2-methoxyethoxy)aluminum hydride. ^fRecovery of S.M. = >23%. ^gNMR yield determined by using an internal standard (CHCl₂CHCl₂).

method provides a useful tool for the construction of functionalized carbon skeletons.

A typical experimental procedure is as follows: to a solution of **12** (40 mg, 0.30 mmol) and **1** (58 mg, 0.36 mmol) in toluene (2.0 ml) was added TMSOTf (0.055 ml, 0.30 mmol) at -78 °C. After the reaction mixture was stirred for 0.5 h at -78 °C, NaCH(CO₂Et)₂, generated from NaH (14 mg, 60% dispersion in mineral oil, 0.36 mmol) and CH₂(CO₂Et)₂ (60 mg, 0.38 mmol) at 0 °C in THF (2.0 ml), was successively added at -78 °C. After stirring for 1 h at -78 °C, the reaction was quenched with phosphate buffer (pH 7) and aqueous layer was extracted with

**Scheme 1.**

CH₂Cl₂. The combined organic layer was washed with H₂O and brine. After removal of the solvent, the resulting residue was purified by preparative TLC to afford the desired product **13** (116 mg, 73%, syn/anti = 29/71).

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References and Notes

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